REMARKS

In accordance with the above amendments, a new Abstract has been proposed to replace one which was objected to by the Examiner. Claims 64-66, 68-70, 117, 122 and 123 (9 claims) have been canceled; claims 59, 62-63, 67, 71-78, 84-93, 115-116 and 120-121 have been amended; and new claims 126-130 (5 claims) have been added. No claim has been allowed.

As indicated above, the Abstract of the disclosure was objected to because it did not adequately describe the claimed invention. Accordingly, a new Abstract has been proposed and is offered in replacement of the earlier Abstract. It is believed this should overcome this rejection.

Certain claims have been objected to because of informalities or obvious errors. With regard to these, claims 66, 68, 117, 122 and 123 have been canceled and claims 59, 62-63, 67, 71-78, 84, 93, 115, 116, 120 and 121 have been amended. It is believed that this should overcome all of the objections in Item 5 of the Official Action.

The amendments to the claims include an extensive amendment to claim 115 which has been amended to specify and clarify what is meant by T_{ck} cells (based on recitation and previous claims 120 and 121) and to specify that the T_{ck} cells have not been contacted by anti-CD3 antibodies. This also more clearly distinguishes these cells from T_{tcr} cells such as those described by Parry et al (cited by the Examiner), as

will be discussed below. It is clear from the application as a whole that this is a feature that distinguishes the two cells types (see, for example, page 6, lines 12-15 and page 13, lines 23-25). In addition, claim 115 has been further amended to clarify the result of the claimed method and its significance, and to include specific method steps as recited in former claim 117 which, accordingly, has been canceled.

New claim 126 is based on previous claim 70 and new claim 127 is based on previous claim 68, both of which have been canceled. It is believed that the language of claim 127 should meet all of the Examiner's objections raised with respect to former claim 68. In particular, the language of claim 127 clarifies the fact that the two populations of cells are treated separately throughout the method. Claim 127 also further defines what is meant by "T_{tcr} cells" which has a basis, for example, in the passage at page 6, lines 9-13. New claim 128 further defines a particular way in which T_{tcr} cells might be produced based on the same passage in the text of the specification.

New claims 129 and 130 are directed to preferred cytokines for producing T_{ck} cells. This finds support, for example, at page 5, lines 19-22.

In Item 6 of the detailed Action, the claims under consideration were rejected under 35 USC § 112, second

paragraph, as being incomplete for omitting essential steps thereby creating a gap between the steps.

Claims 64-66, 68-70, 117 and 122-123 have been canceled thereby leaving claim 115 as the sole independent claim presently having been examined in the present Action. As amended, claim 115 is believed to contain a clear description of all necessary steps in the method. By way of explanation, claim 115 is directed to a method which allows the identification of compounds having efficacy in the treatment of chronic inflammatory disease. The method involves testing the compound for its ability to selectively inhibit the ability of T_{ck} cells to induce pro-inflammatory cytokine release from a monocyte. The claim also now specifies how the results of this testing may be interpreted, i.e., that if the compound is able to achieve such inhibition, this indicates that the compound does have efficacy in the treatment of chronic inflammatory disease.

It is believed clear from the present language of the claim itself that the test must involve inducing the production of cytokines from monocytes using T_{ck} cells, and determining whether the presence of the test compound inhibits this production. The specification (and dependent claim 118) provide a more detailed teaching as to suitable cytokines that could be measured. A more particular test is also set out in more detail in dependent claim 127.

The Examiner has pointed what appears to be perceived as specific deficiencies in the claims. The first involves how inhibition of T_{ck} cells is measured. It should now be clear from the language of the claim that the claimed method measures the inhibition of cytokine release from monocytes stimulated by the T_{ck} cells. Thus, an inhibition of cytokine release from monocytes is what provides a measure of the inhibition of the ability of T_{ck} cells to activate monocytes. The Examiner also asks what inhibition of T_{ck} indicates. The claim has been amended to explicitly state that the relevant inhibition indicates that the compound has efficacy in the treatment of chronic inflammatory disease.

The Examiner has also asked how monocytes are used in this method. It is believed to be clear from the present language of the claim that monocytes are normally induced to produce cytokines by T_{ck} cells and that an active test compound is one which inhibits this effect.

Finally, the Examiner has asked about a fixation step in this method. A fixation step is not an essential feature of the invention and, indeed, is no longer even mentioned in the claims.

Item 7 of the detailed Action rejects the examined claims under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicants regard as the invention. This rejection is respectfully traversed for reasons that follow.

With regard to subpart 7A, independent claim 115 specifies that the T_{ck} cells are produced by incubating a population of T cells with one or more cytokines or are isolated from synovial tissue. As indicated, claim 115 also specifies that the T_{ck} cells have not been contacted with anti-CD3 antibody.

The use of the term "T_{tcr} cells" is further explained in claim 127 in which these cells are defined as T cells that have been activated by triggering of the T cells receptor for antigen. Claim 128 further specifies that this may be achieved using anti-CD3 antibodies.

It is believed that the above amendments add sufficient specificity to justify the use of the abbreviations and overcome the rejection. Accordingly, withdrawal of this rejection is respectfully requested.

With regard to Item 7B, the expression "antibody-like molecule" has been removed from claim 116. With regard to 7C-E, claim 68 has been canceled and the same subject matter has been reintroduced in new dependent claim 127 which specifies that the two cultures are treated separately and that a comparison of the effects of the compound on the two cultures is necessary to reach a conclusion. The language of new claim 127 is believed to be clear and unambiguous.

With regard to Items 7C-F, claims 68 and 122 have been canceled.

In Item 8, it is noted that the examined claims under consideration have been rejected under 35 USC § 102(b) as being anticipated by Parry et al (The Journal of Immunology.1997; 158: 3673-3681). It is the Examiner's position that the reference clearly anticipates the claimed invention. This rejection is respectfully traversed for reasons that follow.

At the outset, it is noted that Parry et al describe two different sets of T cells, both of which have been stimulated with anti-CD3 antibodies. One set is described under the heading "T cell line preparation" on page 3674. These cells are T cell lines which are cultured in the presence of IL-2 and anti-CD3 antibodies. It is specified that this treatment is carried out in order to achieve stimulation. However, this stimulation is achieved by the actions of the anti-CD3 antibodies, not by the action of the IL-2. The IL-2 acts here simply as a growth factor to induce proliferation of the T cells.

Similarly, another set is described in the following passage in Parry et al entitled "T lymphocyte stimulation and fixation" which describes a method by which T cells were stimulated using just anti-CD3 antibodies. Importantly, all

the T cell populations used by Parry et al had therefore been stimulated using anti-CD3 antibodies.

The presence of the anti-CD3 antibodies here means that the cells produced by this stimulation would, in fact, be T_{tcr} cells as described in the present application, not T_{ck} cells. This can be seen from the fact that the cells of Parry et al stimulate monocytes to secrete both IL-10 and TNFα. As explained in the present application, such an effect is characteristic of T_{tcr} cells.

As also explained in the specification, T_{tcr} cells are a completely different group of cells and behave differently from T_{ck} cells.

In order to make this distinction more clear, claim 115 has been amended to specify that the T_{ck} cells have not been contacted with anti-CD3 antibodies. Claim 115 therefore requires the use of T_{ck} cells in the claimed methods, and methods which use only T_{tcr} cells do not fall within the scope of the claim.

Thus, Parry et al only describes T cells which have been stimulated with anti-CD3 antibodies. This method cannot, therefore, anticipate the method of claim 115 and it is requested that this rejection be withdrawn.

In Item 9, claims 115 and 116 have been rejected under 35 USC § 103(a) as being unpatentable over Parry et al, above, in

view of Sebbag et al (Eur. J. Immunol. 1997; 27: 624-632). This rejection is also respectfully traversed.

The subject matter of the present invention is believed to be non-obvious in view of Parry et al in view of Sebbag et al. As explained above, Parry et al do not describe the production or use of T_{ck} cells as required by the present invention. Parry et al does not, therefore, anticipate the present invention. Parry et al, optionally in view of Sebbag et al, does not teach the use of such T_{ck} cells in an assay for compounds having efficacy in the treatment of chronic inflammatory disease, such as rheumatoid arthritis.

Clearly, there are many artificial means that could be used to activate T cells in vitro. However, it is not possible to predict whether any of these will effectively mimic those T cells which are activated *in vivo*. For example, T_{tcr} cells are an example of a type of activated T cells that can be artificially produced (as described by Parry et al). However, based on the teaching of Parry et al, the skilled reader would not know whether those cells would actually be useful in a screening assay for potentially therapeutic compounds.

The present invention is based on the unexpected finding that artificially produced T_{ck} cells are equivalent to the activated T cells present in chronic inflammatory disease, such as T cells from rheumatoid synovial tissue. Artificially

generated T_{ck} cells may be used as a cheap and readily producible alternative to synovial T cells in assay methods as claimed in the present application.

Without the knowledge that these cells are actually equivalent in terms of effector function to the activated T cells found in chronic inflammatory tissue, the skilled person would have no reason to expect that carrying out such an assay method would have any utility in identifying potential therapeutic agents. The effects of a compound on an artificially generated cell line *in vitro* cannot be assumed to have any relevance in relation to the possible effects of that compound *in vivo*.

For example, if the methods of the present invention were carried out using T_{ck} cells, agents could be identified which would inhibit the effects of the T_{tcr} cells on cytokine production by monocytes. However, the skilled person would have no way of knowing whether those compounds would have any effect *in vivo* or whether they might be useful in the treatment of any particular diseases. The skilled person would have no reasonable expectation that the compounds identified in such an assay would be effective. Before the present invention, the same applied to assays which might use T_{ck} cells. Again, the skilled person would have had no reasonable expectation that compounds identified in such an assay would actually be effective *in vivo*. By demonstrating

the equivalence of T_{ck} cells with the activated T cells present in chronically inflamed tissue, the inventors have opened up a new way of identifying potential therapeutic compounds that could be used in the treatment of such chronic inflammation. Thus, this rejection is also believed to have been overcome.

In view of the amendments, taken together with the remarks herein, applicants believe that the objections and rejections raised by the Examiner have been overcome and the Examiner is requested to reconsider and withdraw the present rejections and objections and allow the claims.

Should minor issues remain that, in the opinion of the Examiner, could be resolved by telephone interview, the Examiner is asked to contact the undersigned attorney to attempt to resolve same and expedite prosecution of this application.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment to an Official Action dated February 27, 2006, a Transmittal Letter and a Petition for a three-month extension of time, together with a check in the amount of $1020.00 for the extension fee, in connection with application Serial No. 10/088,801 of inventor(s), Fionula M. Brennan et al., filed September 18, 2002, for "THERAPEUTIC METHODS AND COMPOUNDS" are being sent by first class mail, postage prepaid and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 24, 2006.

Barbara L Davis

Barbara L. Davis
On Behalf of C. G. Mersereau

Date of Signature: August 24, 2006